



## Short Communication

# Impact of Living Donor Liver Transplantation on COVID-19 Clinical Outcomes from a Quaternary Care Centre in Delhi

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## Abstract

**Background and Aims:** The anticipated fear of serious outcomes in coronavirus infected liver transplant recipients led to disruption of transplant services globally. The aim of our study was to analyze COVID-19 severity in transplant recipients and to compare the difference of COVID-19 clinical outcomes in early (<1 year) vs. late (>1 year) post-transplant period. **Methods:** 41 post-living donor liver transplant recipients with COVID-19 infection were studied retrospectively from 1st April 2020 to 28th February 2021. **Results:** The median age was 49.00 years with a male preponderance (80.49%). Fifteen patients had infection within 1 year of transplant and 26 were infected after 1 year of transplant. The overall median interval between transplantation and COVID-19 diagnosis was 816.00 days. Fever and malaise were the common presenting symptoms. The most common associated comorbidities were diabetes mellitus (65.85%) and hypertension (46.34%). The severity of illness was mild in 28 (68.29%), moderate in 4 (9.76%), severe in 6 (14.63%) and critical in 3 (7.32%). To identify associated risk factors, we divided our patients into less severe and more severe groups. Except for lymphopenia, there was no worsening of total bilirubin, transaminases, alkaline phosphatase, and gamma-glutamyl transferase in the more severe group. Eight (19.51%) patients required intensive care unit admission and three (7.32%) died, while none suffered graft rejection. In recipients with early vs. late post-transplant COVID-19 infection, there were similar outcomes in terms of severity of COVID-19 illness, intensive care unit

care need, requirement of respiratory support, and death. **Conclusion:** Living donor liver transplantation can be performed during the COVID-19 pandemic without the fear of poor recipient outcome in cases of unfortunate contraction of severe acute respiratory syndrome coronavirus-2.

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## Introduction

The current coronavirus disease-19 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has witnessed a disruption in transplant activities worldwide. The anticipated fear of potential serious outcome in solid organ liver transplantation, particularly in the perioperative and early postoperative periods, when there is maximal immune suppression, led to this disruption. There is also a possibility of eligible liver donors being infected with SARS-CoV-2 and transmitting the same to their recipients. Furthermore, the added risk of nosocomial infections during hospital stays and follow-up visits put the transplantation program on the back foot. Last year, transplant services were restarted in most centers across the world after an initial suspension and subsequent revamp.<sup>1,2</sup> The emerging reports of increased morbidity and mortality due to COVID-19 infection in patients with chronic liver disease and cirrhosis, as compared to the general population, vs. denial of a timely life-saving transplant procedure in already sick patients poses an ethical dilemma. At the same time, by subjecting these patients to a major liver transplantation procedure followed by iatrogenic immunosuppression, which can lead to the worsening of perioperative and short-term outcomes in case of unfortunate contraction of SARS-CoV-2, needs to be investigated.

Our transplant center is located at Delhi, which is a major hotspot for the COVID-19 pandemic. We restarted our transplant services after an initial period of precaution, with restructuring of COVID safe clinical protocols.<sup>1</sup> While India is currently reeling under the tsunami of the pandemic's 2<sup>nd</sup>

**Keywords:** COVID-19; SARS-CoV-2; Living donor liver transplantation, LDLT; Mortality; Perioperative.

**Abbreviations:** ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; COVID-19, coronavirus disease-19; GGT, gamma-glutamyl transferase; LOR, low oxygen requirement; HOR, high oxygen requirement; ICU, intensive care unit; IQR, interquartile range; LDLT, living donor liver transplantation; LOR, low oxygen requirement; LT, liver transplantation; MV, mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WHO, World Health Organization.

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wave caused by new variants of the SARS-CoV, the data presented here is from the 1<sup>st</sup> wave, which was kinder to the Indian sub-continent compared to the west.<sup>3,4</sup>

The data on outcome of COVID-19 infection in living donor liver transplantation (LDLT) recipients is sparse, with most reports being from the west and involving primarily deceased donor programs. The aim of this study was to investigate the severity of COVID-19 infection in our transplant recipients and to compare the impact of liver transplantation on COVID-19 clinical outcomes in the early (<1 year) vs. late (>1 year) post-transplant period.

## Methods

This was a retrospective observational study of 41 post-LDLT recipients who contracted SARS-CoV-2 infection during the 1<sup>st</sup> wave of the COVID-19 pandemic (1<sup>st</sup> April 2020 to 28<sup>th</sup> February 2021). During this period, a total of 54 LDLT and 3 simultaneous live liver-kidney transplants were conducted at our center, out of which 12 recipients contracted SARS-CoV-2 infection. The remaining 29 were recipients who had been transplanted prior to 1<sup>st</sup> April 2020 and were infected during this time interval.

### Inclusion criteria

All LDLT recipients (age at COVID-19 diagnosis >18 years) being followed up at the BLK-MAX hospital with positive nasopharyngeal swab real time-polymerase chain reaction between 1<sup>st</sup> April 2020 to 28<sup>th</sup> February 2021.

### Exclusion criteria

Recipients with negative real time-polymerase chain reaction test.

### Definitions

The need for respiratory support was categorized as no oxygen, low oxygen requirement (LOR), high oxygen requirement (HOR), and mechanical ventilation (MV). LOR used a nasal cannula hooked up to Venturi mask, with FiO<sub>2</sub> of 0.5. HOR used a Venturi mask, with FiO<sub>2</sub> of 0.6, a reservoir mask with oxygen at 15 L/min, and high-flow nasal ventilation as well as non-invasive ventilation.

Recipients with SARS-CoV-2 infection were further classified into categories of severity per World Health Organization guidelines, as detailed here:<sup>5</sup>

**Mild illness:** Clinical symptoms (e.g., fever, cough, sore throat, malaise, headache, nausea, vomiting, diarrhea, loss of taste and smell) and no radiological evidence of pneumonia.

**Moderate illness:** Fever, respiratory symptoms, and imaging findings of pneumonia.

**Severe illness:** Any of the following: respiratory rate of >30 times per minute, SpO<sub>2</sub> of <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300 mmHg, or lung infiltrates of >50%.

**Critical illness:** Any one of the following: respiratory failure, requirement of mechanical assistance, shock, or "extrapulmonary" organ failure.

### Clinical outcome measures

For the purpose of identifying risk factors and evaluating

their clinical profile, patients were divided into two broad groups, namely less severe and more severe. The less severe group was comprised of those with mild illness and the more severe group was comprised of moderate, severe, and critical illnesses.

To compare COVID-19 clinical outcomes in the early vs. late post-transplant periods, the cohort was divided into two groups. The early period represented when COVID-19 infection was contracted within 1 year of undergoing transplant. The late period was represented when recipients were infected after 1 year past the transplant. The impact of time duration from transplant surgery to SARS-CoV-2 infection was evaluated with respect to degree of requirement of respiratory support, hospital admissions, intensive care unit (ICU) need, COVID-19 illness severity, and mortality.

The institutional review board of Dr. B.L. Kapur Memorial Hospital approved this study protocol (IRB committee/AARCE/July/2021/34), which waived the requirement for informed consent due to the retrospective nature of the study design.

### Statistical analysis

Descriptive statistics are presented in the form of mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. For comparing means of two groups, independent samples *t*-test was used for normally distributed data and Mann-Whitney *U*-test was used for non-normally distributed data. Fisher's exact test was used to test the association between two categorical variables. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA).

## Results

The baseline demographic and clinical characteristics are described as median (range) or frequency (percentage) (Table 1). The majority of the patients were male. The median patient age was 49.00 years (interquartile range [IQR]: 44.00, 60.00) and BMI was 29 kg/m<sup>2</sup> (IQR: 26.00, 31.00). Ethanol was the primary etiology for liver cirrhosis. The median time from liver transplantation to COVID-19 infection was 816.00 days (IQR: 223.00, 2,081.00). All patients presented with fever, with a median temperature of 100.60 °F (IQR: 99.50, 101.00). The next most common presenting symptom was malaise (in 68.29%), and 65.85% had diabetes mellitus while 46.34% had hypertension as comorbidities (Table 1).

The majority of our patients (*n*=27, 65.85%) did not require any oxygen support, while 7 (17.07%) required LOR, 4 (9.76%) required HOR, and 3 (7.3.2%) required MW.

### Observed immunosuppressant strategies and clinical management

Of the 41 recipients, 39 (95.12%) were on tacrolimus and 24 (58.54%) were on oral mycophenolate sodium (Myfortic, Novartis, Wehr, Germany). Tacrolimus was continued without dose alteration in non-hospitalized patients (i.e. those with mild and moderate illness). Those hospitalized underwent minimization of tacrolimus to 1/3rd dose (target level: 4–6 ng/dL). Tacrolimus was withheld in cases of severe illness with underlying or suspected sepsis and in cases of critical illness. The antimetabolite Myfortic was withheld temporarily in all patients with active infection, for a minimum of 2 weeks or until resolution of symptoms.

Eighteen (43.90%) recipients were on baseline mainte-

**Table 1. Clinical and laboratory characteristics of COVID-19 in LDLT recipients**

<b>Factor</b>	<b>Value, n=41</b>
Male sex, <i>n</i> (%)	33 (80.49)
Female sex, <i>n</i> (%)	8 (19.51)
BMI in kg/m <sup>2</sup> , median (IQR)	29.00 (26.00, 31.00)
Age in years at diagnosis of COVID-19, median (IQR)	49.00 (44.00, 60.00)
Days from LT to COVID-19, median (IQR)	816.00 (223.00, 2,081.00)
Perioperative SAR-CoV-2 diagnosis within 30 days	3 (7.3)
Primary etiology, <i>n</i> (%)	
Ethanol	17 (41.46)
Hepatitis B	9 (21.95)
Nonalcoholic fatty liver disease	8 (19.51)
Hepatitis C	4 (9.76)
Others	3 (7.32)
Hepatocellular carcinoma, <i>n</i> (%)	7 (17.50)
Hospital-acquired SARS-CoV-2, <i>n</i> (%)	3 (7.32)
Severity of COVID-19, <i>n</i> (%)	
Mild	28 (68.29)
Moderate	4 (9.76)
Severe	5 (14.63)
Critical	3 (7.32)
SpO <sub>2</sub> lowest %, median (IQR)	96.00 (94.00, 98.00)
COVID symptoms	
Fever (maximum temperature in °F), median (IQR)	100.60 (99.50, 101.00)
Malaise, <i>n</i> (%)	28 (68.29)
Cough, <i>n</i> (%)	14 (34.15)
Difficulty in breathing, <i>n</i> (%)	12 (29.27)
Sore throat, <i>n</i> (%)	11 (26.83)
GI symptoms, <i>n</i> (%)	6 (14.63)
Loss of smell, <i>n</i> (%)	4 (9.76)
Loss of taste, <i>n</i> (%)	2 (4.88)
Comorbidities, <i>n</i> (%)	
Diabetes mellitus	27 (65.85)
Hypertension	19 (46.34)
Chronic kidney disease	1 (2.44)
Malignancy	1 (2.44)
Total admissions, <i>n</i> (%)	14 (34.15)
ICU, <i>n</i> (%)	8 (19.51)
Oxygenation, <i>n</i> (%)	
Room air, <i>n</i> (%)	27 (65.85)
LOR, <i>n</i> (%)	7 (17.07)
HOR, <i>n</i> (%)	4 (9.76)
MV, <i>n</i> (%)	3 (7.32)
Laboratory assessment at time of diagnosis, median (IQR)	
Lowest ALC recorded as ×10 <sup>3</sup> cells/μL	1.20 (0.80, 1.60)

(continued)

Table 1. (continued)

Factor	Value, n=41
Total bilirubin as upper limit of normal 1.3 mg/dL	0.80 (0.50, 1.20)
Peak AST as upper limit of normal 40 U/L	44.00 (31.00, 55.00)
Peak ALT as upper limit of normal 50 U/L	47.00 (29.00, 83.00)
ALP as upper limit of normal 130 U/L	120.00 (94.93, 198.00)
GGT as upper limit of normal 60 U/L	76.00 (45.00, 158.00)
Peak creatinine in mg/dL	0.98 (0.83, 1.21)
Immunosuppression, n (%)	
Pre-COVID-19 infection tacrolimus	39 (95.12)
During COVID-19 tacrolimus continued	31 (79.49)
Mycophenolic acid	24 (58.54)
Oral steroids	18 (43.90)
Bolus steroids	11 (26.83)
Everolimus	6 (14.63)
Everolimus continued	4 (9.75)
Class of antibiotics, n (%)	
Azithromycin	10 (24.39)
Meropenem	8 (19.51)
Cefuroxime	6 (14.63)
Piperacillin/tazobactam	2 (4.88)
Levofloxacin	1 (2.44)
Other medications, n (%)	
Ecosprin at 75 mg	29 (70.73)
Rivaroxaban	17 (41.46)
Enoxaparin	14 (34.15)
CPT	5 (12.20)
Remdesivir	5 (12.20)

LDLT, living donor liver transplantation; COVID-19, coronavirus disease-19; BMI, body mass index; IQR, interquartile range; ICU, intensive care unit; LT, liver transplantation; SAR-CoV-2, severe acute respiratory syndrome coronavirus-2; SpO<sub>2</sub>, oxygen saturation; LOR, low oxygen requirement; HOR, high oxygen requirement; MV, mechanical ventilation; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; ALC, absolute lymphocyte count; CPT, convalescent plasma therapy.

nance oral prednisolone pre-COVID-19. Our strategy was to double the oral steroid on a case-to-case basis, with a maximum ceiling dose of 20 mg/day. Of the 14 (34.15%) patients who needed admission, injectable steroids were administered in 11 (26.83%) patients.

None of the patients developed acute cellular rejection during the COVID-19 illness with our immunosuppressant strategies. One recipient underwent percutaneous liver biopsy for suspected acute rejection, which was subsequently diagnosed as severe steatosis.

In total, 65.85% patients received antibiotic prophylaxis. Five (12.20%) patients received convalescent plasma therapy (CPT), and remdesivir was given to five (12.20%) patients, out of which three received both CPT and remdesivir. Four patients in severe illness category and one patient with critical illness received CPT and /or remdesivir, with complete recovery of four of the severely ill patients. In total, 29 (70.73%) and 17 (41.46%) patients were on ecosprin and rivaroxaban, respectively, and 11 received both; injected enoxaparin was started in all admitted patients. None of our patients received ritonavir, hydroxychloroquine, ivermectin or tocilizumab.

The potential risk factors impacting the severity of COVID-19 illness were analyzed. In total, 28 (68.29%) patients were classified into the less severe group and 13 (31.7%) patients were classified into the more severe group. The two groups were similar in age, BMI, sex, primary etiologies, and comorbidities (Table 2). Control for comorbidities like diabetes mellitus and hypertension was not carried out in this study, as they were not found to be associated with severity of COVID-19 infection in our bivariate analysis (Table 2). In both groups, total bilirubin levels (0.71 mg/dL vs. 0.80 mg/dL,  $p=0.70$ ), aspartate aminotransferase (AST) (47.00 IU/L vs. 40.00 IU/L,  $p=0.50$ ), alanine aminotransferase (ALT) (48.50 IU/L vs. 40.00 IU/L,  $p=0.39$ ), alkaline phosphatase (ALP) (130.50 U/L vs. 108.00 U/L,  $p=0.64$ ), gamma-glutamyl transferase (GGT) (76.50 U/L vs. 61.00 U/L,  $p=0.79$ ), and creatinine (0.98 mg/dl vs. 0.90 mg/dl,  $p=0.99$ ) at admissions were comparable, and thus were not affected by severity. Only the absolute lymphocyte count ( $1.40 \times 10^3/\mu\text{L}$  vs.  $0.65 \times 10^3/\mu\text{L}$ ,  $p<0.001$ ) was significantly lower in the more severe group (Table 2). In the patients who required ICU admission, the absolute lymphocyte count was significantly lower than in the group who did not require ICU care

**Table 2. Risk factors and clinical profile in the less severe (mild) and the more severe (moderate, severe, and critical) group**

Factors	Less severe group, n=28	More severe group, n=13	<i>p</i>
Age in years at diagnosis of COVID-19, median (IQR)	49.50 (41.00, 59.00)	49.00 (45.00, 61.00)	0.60
Sex, <i>n</i> (%)			0.69
Male	23 (82.14)	10 (76.92)	
Female	5 (17.86)	3 (23.08)	
BMI, median (IQR)	28.00 (25.50, 31.50)	29.80 (27.00, 30.70)	0.80
Primary etiology, <i>n</i> (%)			0.89
Ethanol	12 (42.86)	5 (38.46)	
Hepatitis B	7 (25.00)	2 (15.38)	
Non alcoholic fatty liver disease	5 (17.86)	3 (23.08)	
Hepatitis C	2 (7.14)	2 (15.38)	
Others	2 (7.14)	1 (7.69)	
Comorbidities, <i>n</i> (%)			
Diabetes mellitus	16 (57.14)	11 (84.62)	0.16
Hypertension	12 (42.86)	7 (53.85)	0.74
Laboratory assessment at time of diagnosis, median (IQR)			
ALC recorded as $\times 10^3$ cells/ $\mu$ L	1.40 (1.00, 1.77)	0.65 (0.30, 0.90)	<0.001
Peak creatinine in mg/dL	0.98 (0.84, 1.06)	0.90 (0.76, 1.36)	0.99
Total bilirubin upper limit of normal 1.3 mg/dL	0.71 (0.48, 1.27)	0.80 (0.50, 1.00)	0.70
Peak AST upper limit of normal 40 U/L	47.00 (32.00, 53.50)	40.00 (22.00, 72.00)	0.50
Peak ALT upper limit of normal 50 U/L	48.50 (39.50, 78.50)	40.00 (21.00, 84.90)	0.39
ALP upper limit for normal 130 U/L	130.50 (96.47, 192.00)	108.00 (78.30, 248.00)	0.64
GGT upper limit of normal 60 U/L	76.50 (45.00, 140.00)	61.00 (43.00, 158.00)	0.79
Medicines, <i>n</i> (%)			
Oral steroid	12 (42.86)	6 (46.15)	1.00
Pre-COVID-19 tacrolimus	27 (96.43)	12 (92.31)	0.54

Mann-Whitney *U*-test and Fisher's test were used to compare samples and proportions, as appropriate. Italicized values indicate *p*-values less than 0.05 (for visual purposes). COVID-19, coronavirus disease-19; BMI, body mass index; IQR, interquartile range; ALC, absolute lymphocyte count; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

( $0.47 \pm 0.31 \times 10^3/\mu\text{L}$  vs.  $1.39 \pm 0.57 \times 10^3/\mu\text{L}$ ,  $p=0.001$ ).

In total, 15 (36.58%) and 26 (63.42%) post-transplant recipients were infected during the early period (<1 year) and the late period (>1 year) respectively (Fig. 1). The need for oxygen was similar in both the groups; the early group involved LOR in 19.23%, HOR in 7.69%, and MV in 7.69%, and the late group involved LOR in 13.33%, HOR in 13.33%, and MV in 6.67%. Hospital admission was 46.67% and 26.92%, respectively, in the early and late groups, and 4 recipients in each group required ICU admission. The overall mortality involved 3 (7.32%) patients, out of which 1 (6.67%) death occurred in the early period and 2 (7.69%) deaths occurred in the late post-transplant period (Table 3).

Transplant patients who were not admitted were instructed to self-isolate, monitor temperature daily, and scheduled for weekly electronic follow-up and WhatsApp video calls to avoid face-to-face consultations.

## Discussion

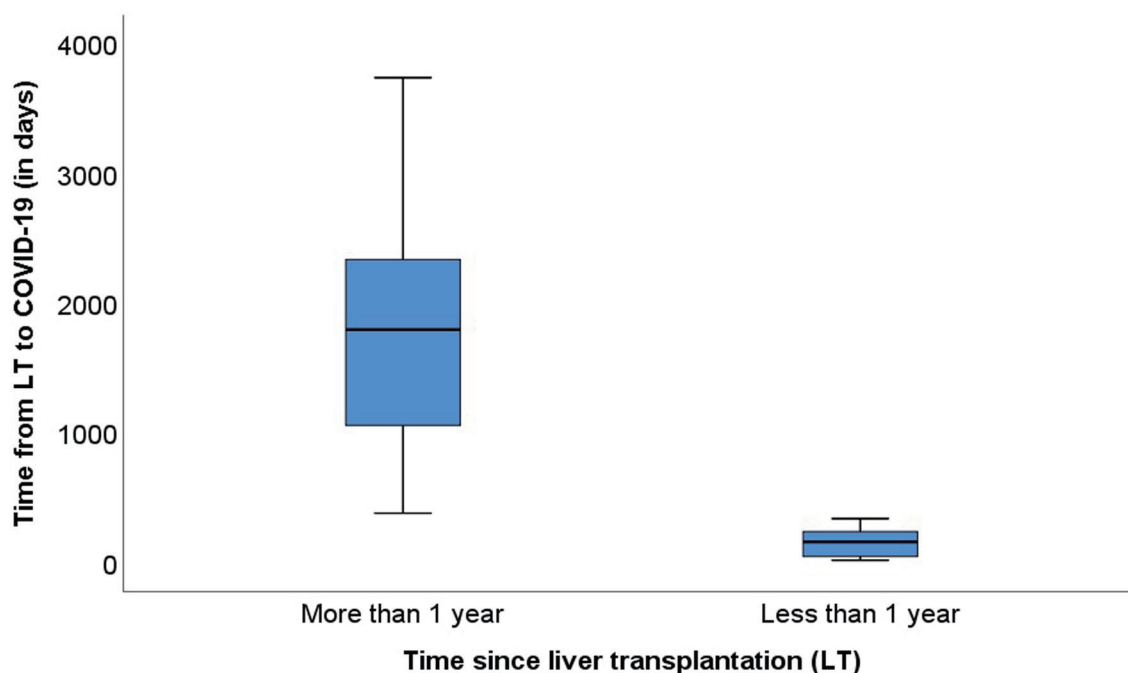
In our study, we included transplant recipients who contracted SARS-CoV-2 during the 1st wave of the pandemic

(1st April 2020 till 28 Feb 2021). The SARS-CoV-2 delta variant (lineage B.1.617.2), which was first detected in India in October 2020 and named as the Delta variant on 31 May 2021 by the WHO, was identified as the primary cause of the 2<sup>nd</sup> wave (beginning from mid-March 2021 and ongoing).<sup>6</sup> As genome sequences of our patients were not done to determine the causative variant, we retrospectively infer that most of our recipients could have been infected with the alpha variant, which was responsible for the 1<sup>st</sup> wave.

The impact and outcomes of SARS-CoV-2 infection in LDLT recipients is still evolving. Herein, we discuss a single-center experience of 41 post LDLT recipients who contracted SARS-CoV-2 infection. Our study predominately consisted of nonelderly (<60 years old) male LDLT recipients.<sup>7-9</sup> The comorbidities in our group were similar to other registries which were primarily comprised of deceased donor recipients. Two-thirds of our patients were successfully managed with home quarantine. Only 19.51% of our patients required ICU admission and 7.32% required MV.

Hepatocellular injury was not more frequent in our more severe group, in consonance with most center reports.<sup>10</sup> None of our patients had new onset of acute kidney injury during their course of COVID-19 illness.





**Fig. 1. Time from liver transplantation to COVID-19 infection.** COVID-19, coronavirus disease-19.

The overall mortality was 7.32%, which was less than the reported mortality of 18% to 20% in two large cohort registries.<sup>7,9</sup> In the study group reported by Bhoori *et al.*,<sup>11</sup> which was predominantly comprised of long-term liver transplant recipients (>10 years), the authors noted a mortality of 30%, which could be attributed to older age and presence of coexisting multiple comorbidities. The median age in our study was more than a decade younger than these large

cohort registries, which could be the possible reason for the lower rate of ICU admission and lower mortality rate, despite half of our patients having associated comorbidities.

The other reasons for overall favorable outcome in our patients could be the immunosuppressant protocol. Calcineurin inhibitors (CNIs) were not discontinued, except in critical COVID-19 cases and in recipients with suspected nonviral sepsis, as such was reported to be associated with better

**Table 3. Association of time from liver transplantation and COVID-19 clinical outcome**

Factors	Time of liver transplantation to COVID-19 infection		p
	Less than 1 year, n=15	More than 1 year, n=26	
Severity of COVID-19 illness, n (%)			0.43
Mild	9 (60.00)	19 (73.08)	
Moderate	3 (20.00)	1 (3.85)	
Severe	2 (13.33)	4 (15.38)	
Critical	1 (6.67)	2 (7.69)	
Outcome, n (%)			
Recovered	14 (93.33)	24 (92.31)	1.00
Died	1 (6.67)	2 (7.69)	
Total admissions, n (%)	7 (46.67)	7 (26.92)	0.31
ICU, n (%)	4 (26.67)	4 (15.38)	0.43
Oxygenation, n (%)			0.89
Room air	10 (66.67)	17 (65.38)	
LOR	2 (13.33)	5 (19.23)	
HOR	2 (13.33)	2 (7.69)	
MV	1 (6.67)	2 (7.69)	

Mann-Whitney U-test and Fisher’s exact test were used to compare samples and proportions, as appropriate. COVID-19, coronavirus disease-19; ICU, intensive care unit; LOR, low oxygen requirement; HOR, high oxygen requirement; MV, mechanical ventilation.

outcomes; moreover, CNIs have been found to inhibit SARS-CoV in a dose-dependent manner in *in vitro* studies.<sup>12,13</sup>

The antimetabolite Myfortic was temporarily withdrawn in all patients, as continuation of mycophenolate mofetil was associated with poor outcomes in various studies; furthermore, it could worsen COVID-associated lymphopenia.<sup>7,14</sup> Early temporary withdrawal of Myfortic could be the reason for the low incidence of diarrhea in our cohort (14.63%). Up to 43.9% of our recipients were on oral minimal maintenance steroids pre-COVID. In liver transplant recipients on oral steroids, their dosage was doubled to cover the potential risk of rejection when antimetabolites were on hold; this strategy became more prevalent during the 2<sup>nd</sup> half of 2020, as emerging reports suggested benefit of glucocorticoid to attenuate the effect of cytokine storm.<sup>15</sup> The use of steroids in mild to moderate COVID-19 (not requiring any respiratory support) is not recommended; nevertheless, we continued such in recipients who were already on oral corticosteroids, with a dose equivalent to half the recommended dose of dexamethasone (6 mg) in COVID pneumonia.<sup>15</sup> Whether the use of steroids resulted in halting the disease progression and the need for oxygen supplements needs to be further evaluated in patients on persistent immunosuppressants.

The transplant activity decreased in most of the centers last year during the pandemic. Since the current wave continues to wax and wane, denying a timely life-saving procedure for these sick decompensated cirrhotics awaiting transplant, particularly in those with a potential live donor, may not be justified. International registries have consistently reported increased COVID-19-related mortality in cirrhotics compared to non-cirrhotics and the trajectory of COVID-19 adverse events increased with higher Child-Pugh score.<sup>16,17</sup> Paradoxically, various studies did not show an increased risk of mortality in immunosuppressed liver transplant recipients compared to matched general population following SARS-CoV-2 infection.<sup>7,9</sup> Most of these reports are from recipients transplanted before the pandemic and, hence, they cannot be extrapolated to recipient outcomes for those transplanted during the pandemic.

Most published reports predominately deal with deceased donor recipients who contracted SARS-CoV-2 infection years after LT. In an early Spanish liver transplantation registry report 13.5% (15 of total 111) liver recipients had early posttransplant (<1 year) COVID-19 infection while we had 36.58% (15 of total 41) in the early post-transplant group.<sup>7</sup> Our study demonstrated that COVID-19 clinical outcomes in early (<1 year) post-transplant were not inferior to late (>1 year) post-transplant recipients. The proportion of hospital admissions and ICU care was more in the early post-transplant group, although it was not statistically significant. There was no difference in terms of mortality, oxygen supplementation and MV. This is in contrast to the recent findings of the COVIDSOT working team, which identified the early post-transplant infection (<6 months) as a novel risk factor for increased mortality and need for ICU admission in all solid organ transplant (SOT) recipients. However, separate organ specific subgroup analysis of outcomes was not mentioned in which the liver transplant subgroup constituted 50 (23.8 %) of the total 210 SOT recipients.<sup>18</sup>

In the early post-transplant period, the 1<sup>st</sup> perioperative week is the crucial phase during which liver transplant recipients recover from cirrhosis-associated immune dysfunction, effects of prolonged anesthesia, multiple blood and product transfusion, and surgical trauma.<sup>19,20</sup> Since there is no clear consensus on the definition of perioperative period in LT, any COVID-19 infection occurring up to postoperative day 30, was considered as critical time zone of COVID-19 infection. A cautious approach and COVID-safe protocols need to be followed, since the failure to

detect SARS-CoV-2 infection during this perioperative incubation period or asymptomatic state can lead to rapid progression of COVID-19 illness.<sup>21</sup> There is a paucity of data regarding the outcome of living donor recipients with COVID-19 infection during the perioperative period. There are conflicting sporadic reports of successful recovery of recipients who contracted early COVID-19 after LT. Masoumi *et al.*<sup>22</sup> described good outcome in five patients with early COVID-19 (range 11–68 days) after LT; in addition, three had mild cases, while two had moderate diseases. Contrary to this report, Waisberg *et al.*<sup>23</sup> described their experience of seven patients with early COVID-19 (range of 9–39 days) after LT in which three recipients had severe disease and two died. Notably, their outcome was adversely impacted by their patients' older age, obesity, and associated comorbidities. However, important to note is that most infections reported were after the 1<sup>st</sup> week post-LT. Similarly, in our study three recipients contracted COVID-19 during the 3<sup>rd</sup> and 4<sup>th</sup> postoperative week (1 severe, 1 moderate and 1 mild case), none expired due to COVID-19 pneumonia; possibly, the impact of early 1<sup>st</sup> week perioperative stress was crossed. The highly cited 1<sup>st</sup> grim report from Wuhan of a fatal outcome of a liver transplant recipient due to failure-to-be-detected during the perioperative work-up should not be ignored.<sup>24</sup> Following the point from all major guidelines, the stringent preoperative testing for SARS-CoV-2 with at least two negative reports and the 2<sup>nd</sup> negative report less than 48 h before the surgery was followed by our center.<sup>1,25</sup> We infer that crossing this perioperative bridge without SARS-CoV-2 infection will be the most important milestone in prevention of poor outcome of COVID-19 infection.

The limitations of our study were small sample size and data from a single center. However, our study certainly makes an important contribution to the evolving data on COVID-19 in LDLT recipients reported in the literature. Also, our study may have suffered from underreporting for asymptomatic positives or milder symptoms not being reported. The time is ripe for a large multicentric study from centers with primarily LDLT programs, which will help in addressing and possibly resolving the pertinent issues related to LDLT recipients with COVID-19 illness.

## Conclusions

In our study of LDLT recipients with COVID-19 infection, most of our recipients had only mild illness and did not require hospital admission. Notably, based on our observations, we infer that COVID-19 clinical outcomes in the early vs. late post-transplant period are similar, with the early group not having a severe course, as expected. In case of unfortunate perioperative contraction of SARS-CoV-2 infection, recipients can be successfully navigated towards recovery. Hence, postponing life-saving liver transplantation is not justified in these patients with debilitating illness. Further data will throw light on the COVID-19 clinical outcome in the 1<sup>st</sup> perioperative week. The continuation of steroids and tacrolimus with dose modification during the active phase of infection may attenuate COVID-19 severity.

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### Conflict of interest

The authors have no conflict of interests related to this publication.

### Author contributions

Conceptualization (AC, IJ, AK), data curation (IJ, PL, GS, AG, NK), formal analysis (IJ, SS, AC), writing of the original draft (IJ, AC, AS), critical revision of the manuscript for important intellectual content (AC, MW, AJ), and administrative and study supervision (AC, MW).

### Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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